The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOSEPH A. HEDRICK,
THEODORE R. SANA, J. FERNANDO BAZAN,
and ROBERT A. KASTELEIN

MAILED
SEP 22 2005
U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 2005-1922
Application No. 09/770,528

ON BRIEF

Before SCHEINER, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to compounds, such as antibodies, that bind a mouse interleukin-1 protein. The examiner has rejected the claims as lacking patentable utility. We have jurisdiction under 35 U.S.C. § 134. We reverse, because the evidence of record shows that the disclosed interleukin is likely to be involved in inflammation.

Background

The specification discloses "two novel mammalian, e.g., rodent interleukin-1 like molecules, designated interleukin-1δ (IL-1δ) and interleukin-1ε (IL-1ε). Both IL-1δ and IL-1ε exhibit both structural and sequence similarity, e.g., by homology comparison to known members of the IL-1 family of molecules." Page 5. The specification describes

the "complete nucleotide (SEQ ID NO:1) and corresponding amino acid sequence (SEQ ID NO:2) of a rodent IL-1δ coding segment." Page 16. See also page 22 (SEQ ID NO:2 is "mouse IL-1δ").

"Structural alignment of mouse IL-1δ and mouse IL-1ε with other members of the IL-1 family show[s] conserved features/residues, particularly 12 β strands folded into a β-trefoil fold." Page 40. "The solved structures for IL-1β, the natural IL-1 receptor antagonist (IL-1Ra), and a co-structure of IL1Ra/IL-1 receptor type I . . . suggest how to make a mouse IL-1δ or IL-1ε antagonist. . . . [T]he only known antagonist to IL-1 receptor (IL-1Ra . . .) is missing an amino acid domain bounded by the β4 and β5 strands. . . [,] suggesting that its absence confers antagonist activity." Page 41. "The corresponding loop in rodent IL-1δ or IL-1ε (between β4 and β5) defines a domain that forms a polypeptide loop which is part of a primary binding segment to the IL-1 receptor. . . . More precisely, the loop is defined for IL-1δ by amino [acid] residues Pro47-Ala53 of SEQ ID NO:2. . . . Accordingly, IL-1δ or IL-1ε antagonist activity should be generated by removal of all or an appropriate portion of amino acids located between β4 and β5." Page 42.

The specification discloses that "[t]he IL-1δ or IL-1ε proteins will have a number of different biological activities, e.g., in the immune system, and will include inflammatory functions or other innate immunity responses." Page 31. "The activities of the mouse IL-1α, IL-1β, and IL-1γ have been compared as to their activity to induce IFN-γ [interferon gamma]. . . . The IL-1γ was found to be much more potent in stimulating IFN-1γ [sic, IFN-γ] than either IL-1α or IL-1β. IL-1δ and IL-1ε and their agonists or antagonists should have related activities, typically affecting similar immune functions, including inflammatory responses." Id.

"The family of interleukins 1 contains molecules, each of which is an important mediator of inflammatory disease." Page 97. "IL-1δ or IL-1ε being homologous members of the IL-1 family . . . likely play a role in modulating of local and systemic inflammatory processes . . . , through the enhancement of blood flow, induction of chemoattractants, and the enhancement and adherence of adhesion molecules resulting in the accumulation of inflammatory cells such as macrophages and neutrophils at the site of inflammation." Page 79.

"IL-1δ or IL-1ε are also likely to play a role in systemic inflammatory reactions. . . . A systemic reaction such as septic shock involves vasodilation, due to IL-1, most likely in combination with other cytokines. . . . The newly described IL-1δ or IL-1ε are also likely to be similarly involved." Page 80.

Discussion

1. Claim construction

Claim 7, the only independent claim on appeal, reads as follows:

> 7. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a mature polypeptide comprising at least 8 contiguous amino acid residues from SEQ ID NO:2, wherein said antigen binding site specifically binds an epitope located within said contiguous amino acid residues.

Claim 7 is directed to a binding compound comprising at least an antigen-binding site, where the antigen-binding site is from an antibody that specifically binds a "mature polypeptide" comprising at least eight contiguous amino acids of SEQ ID NO:2, and the epitope bound by the antigen-binding site is located within the contiguous amino acids from SEQ ID NO:2. Claim 7 therefore encompasses, among other things, antibodies that bind specifically to mouse IL-1δ (i.e., the protein having the amino acid sequence shown in SEQ ID NO:2).

2. Utility

The examiner rejected claims 7-9 and 20-25, all of the claims remaining, under 35 U.S.C. §§ 101 and 112, first paragraph, for lack of patentable utility. The examiner bears the initial burden of showing that a claimed invention lacks patentable utility. See In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence.").

The Supreme Court addressed § 101's utility requirement in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). The claimed invention in Brenner "a chemical process which yields an already known product whose utility—other than as a possible object of scientific inquiry—ha[d] not yet been evidenced." Id. at 529, 148 USPQ at 693. The Brenner Court held that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695.

The Court of Customs and Patent Appeals first applied Brenner in In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). The invention claimed in Kirk was a set of steroid derivatives said to have valuable biological properties and to be of value "in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice." Id. at 938, 153 USPQ at 50. The court held that such uses did not satisfy § 101: "There can be no doubt that the insubstantial, superficial

nature of vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher' was recognized, and clearly rejected, by the Supreme Court" in Brenner. See Kirk, 376 F.2d at 945, 153 USPQ at 55.

More recently, the Federal Circuit held that § 101 was not satisfied by a disclosure that "solid granules of polypropylene could be pressed into a flexible film with a characteristic infrared spectrum and that the polypropylene was 'plastic-like.'" In re Ziegler, 992 F.2d 1197, 1203, 26 USPQ2d 1600, 1605 (Fed. Cir. 1993). "Ziegler did not assert any practical use for the polypropylene or its film, and Ziegler did not disclose any characteristics of the polypropylene or its film that demonstrated its utility." Id. "[A]t best, Ziegler was on the way to discovering a practical utility for polypropylene at the time of the filing." Id., 26 USPQ2d at 1605.

On the other hand, the CCPA reversed a rejection for lack of utility in In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980), where the claimed pharmaceutical compositions were disclosed to be useful in treating acute myeloblastic leukemia. The active ingredients in the compositions were closely related to compounds which were "well recognized in the art as valuable for use in cancer chemotherapy" and the evidence showed that the claimed compositions were effective in treating tumors in a mouse model. See id. at 1323-24, 206 USPQ at 887-88.

The Federal Circuit held in Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), that in some circumstances, in vitro testing is sufficient to show utility. More specifically, evidence showing successful in vitro testing supplemented by similar in vitro and in vivo activities of structurally similar compounds was held to meet the requirements of § 101. Id. at 1051, 224 USPQ at 748.

Finally, in In re Brana, the Federal Circuit held that § 101 was satisfied by disclosure that the claimed compounds had higher antitumor activity than related compounds known to have antitumor activity and evidence of in vivo activity against tumors in a mouse model. See 51 F.3d at 1567, 34 USPQ2d at 1442.

Several lessons can be drawn from these cases. First, § 101's requirement that an invention be "useful" is not to be given its broadest reach, such that little or nothing of a chemical nature would be found to lack utility. See Brenner, 383 U.S. at 530, 148 USPQ at 694. Thus, not every "use" that can be asserted will be sufficient to satisfy § 101.

Rather, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. Brenner, 383 U.S. at 534-35, 148 USPQ at 695. Under this standard, § 101 is satisfied by pharmaceutical compositions useful for treating leukemia (Jolles); by evidence showing successful in vitro testing supplemented by similar in vitro and in vivo activities of structurally similar compounds (Cross); and by evidence showing in vivo antitumor activity in mice, combined with a disclosure that the claimed compounds had higher antitumor activity than a known, related compound (Brana).

By contrast, "vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher'" do not satisfy § 101 (Kirk). Likewise, disclosing polypropylene that is "plastic-like" and can be pressed into a flexible film showed that the applicant was "at best . . . on the way to discovering a practical utility for polypropylene at the time of the filing," but not yet there (Ziegler).

In this case, the examiner took the position that the "assertion that the disclosed IL-1δ protein has biological activities similar to known IL-1 polypeptides cannot be

accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities." Examiner's Answer, page 5. The examiner cited several examples of proteins that have different activities despite belonging to the same family of growth factors. Id., pages 5-6. The examiner also pointed to the specification's statement that the IL-1 "family of genes have been implicated in a broad range of biological functions," and Kumar's[1] disclosure that "IL-1δ is an antagonist of IL-1ε, even though both polypeptides belong to the IL-1 family." Id., page 5.

The examiner also cited several references as evidence that "the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." Id., pages 7-8. She concluded that

> based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality for new members of cytokine or growth factor polypeptide families, the assertion that the IL-1δ polypeptide recited in the claims has activities similar to previously characterized IL-1 polypeptides is not substantial.

Id., page 8.

The examiner found the specification's statement that IL-1δ "likely play[s] a role in modulating of local and systemic inflammatory processes" to be nonspecific and insubstantial. See id. at pages 8-9. The examiner found the asserted use in therapy to be insubstantial because the specification does not state what role IL-1δ plays in inflammation or what type of inflammation involves IL-1δ. The examiner found the asserted utility to be nonspecific because "a diverse group of chemical and

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[1] Kumar et al., "Identification and initial characterization of four novel members of the interleukin-1 family,"

environmental stimuli can be said to 'play a role in modulating of local and systemic inflammatory processes', including cytokines, aspirin, lye, scratches, and ice." Id., page 9.

Appellants argue that "the specification discloses at least one specific utility for IL-1δ in inflammation based on structural homology to the IL-1 family and supported by the evidence of record," and that this utility is both substantial and credible. Appeal Brief, page 7. In support of the specification's assertion that IL-1δ is involved in inflammation, Appellants rely on the structural similarity between IL-1δ and other members of the IL-1 family, and on evidence provided by the Kumar and Debets[2] references, which were published after the filing date of this application.

The examiner acknowledged that "[t]here is little doubt that IL-1δ is a new member of the IL-1 family of cytokines, and that all of the IL-1 polypeptides characterized to date play a role of some sort in inflammation," but noted that "these roles are diverse." Examiner's Answer, page 16. See also page 20:

> The specification merely states that IL-1δ is likely to play a role in modulating inflammation. It does not characterize that role. . . . Is it up-regulated or down-regulated during inflammation? Without this information, the skilled artisan would not know if it was desirable to identify drugs that agonize or antagonize IL-1δ as a treatment for inflammation. Does IL-1[δ] play a role in skin inflammation or pancreas inflammation, or inflammation of any other tissue? Without this information, the skilled artisan would have to conduct experiments to identify specific inflammatory responses that involve IL-1δ.

The examiner considered Appellants' post-filing evidence but found that it did not cure the asserted deficiencies. See the Examiner's Answer, page 17:

Journal of Biological Chemistry, Vol. 275, pp. 10308-10314 (2000).

[2] Debets et al., "Two novel IL-1 family members, IL-1δ and IL-1ε, function as an antagonist and agonist of NF-κB activation through the orphan IL-1 receptor-related protein 2," Journal of Immunology, Vol. 167, pp. 1440-1446 (2001).

> The assertion in the specification that IL-1δ is likely to play a role in the modulation of inflammation is not a specific assertion of utility. . . . The post-filing date references of Debets et al. and Kumar et al. constitute specific disclosures of what IL-1δ's role in inflammation is. Unfortunately, these specific roles are not asserted in the specification as originally filed.

See also page 24: "Debets et al. and Kumar et al. provide further characterization of the IL-1δ protein which provide a credible, specific and substantial utility for IL-1δ. This further characterization, however, is part of the act of invention and until it was undertaken, Appellant's claimed invention as disclosed in the specification as originally filed, was incomplete."

The issues raised by the examiner are important ones in the analysis of whether an invention is supported by an adequate utility. If a specification merely discloses that a protein may be involved in one of a multitude of biological activities, or may have some uncharacterized role in any of a variety of diseases, the disclosure may very well fail to meet the requirements of § 101.

In this case, however, we do not find the examiner's concerns to be warranted. The specification states that IL-1δ, to which the claimed product binds, is a member of the IL-1 family of cytokines. The specification also states that all known IL-1 family members play a role in inflammation. The examiner has agreed with both of these points. See the Examiner's Answer, page 16 ("There is little doubt that IL-1δ is a new member of the IL-1 family of cytokines, and that all of the IL-1 polypeptides characterized to date play a role of some sort in inflammation.").

The examiner's rejection, therefore, has little to do with the concerns she has expressed regarding the difficulty of predicting function from structure and the possibility that small changes in protein structure will result in large changes in function. Rather, the rejection seems to be based on the lack of disclosure regarding the specific role that

IL-1δ plays in inflammation – does it contribute to or inhibit inflammation? – and the specific tissue(s) in which it acts.

We do not find these concerns to be adequate to support the rejection. Once it has been accepted that IL-1δ either contributes to or inhibits the inflammatory response, it seems that those skilled in the art would recognize the claimed binding compounds as useful. Specifically, if IL-1δ contributes to inflammation, those skilled in the art would recognize the claimed compounds to be useful in inhibiting inflammation. On the other hand, if IL-1δ inhibits inflammation, those skilled in the art would recognize the claimed compounds to be useful in promoting inflammation.

Thus, it would seem that the examiner's acceptance of IL-1δ as having a role in inflammation would require recognizing that IL-1δ-binding compounds are useful for either inhibiting or promoting inflammation. The examiner has not argued that compounds that promote inflammation lack utility, or that compounds that inhibit inflammation lack utility. Since the examiner apparently accepts that the claimed compounds will have one of these two activities, the disclosure that IL-1δ has a role in inflammation seems adequate to support utility.

The examiner, in fact, has indicated that if the specification had included the more specific disclosures in the Kumar and Debets references, the claims would be supported by an adequate utility. See the Examiner's Answer, page 24. The examiner discounted the references, however, because they were published after this application's effective filing date. Id.

We agree with the examiner that utility must be shown as of the effective filing date. See In re Brana, 51 F.3d at 1567 n.19, 34 USPQ2d at 1441 n.19. However, post-filing evidence is acceptable where it is relied on, not to supplement the specification's

disclosure, but to show the accuracy or inaccuracy of a statement in the specification. See id.; see also In re Hogan, 559 F.2d 595, 605 n.17, 194 USPQ 527, 537 n.17 (CCPA 1977).

Here, we agree with Appellants that the post-filing evidence supports the utility disclosed in the specification. In particular, Debets provides evidence supporting the specification's disclosure that IL-1δ plays a role in inflammation. Debets shows that IL-1δ specifically antagonizes the activity of IL-1ε, inhibiting the inflammatory response that IL-1ε stimulates. See page 1443. Debets also discloses that expression of IL-1δ and IL-1ε is increased in psoriatic skin lesions, "confirm[ing] the involvement of these novel IL-1s in response to skin inflammation." Page 1445.

It is true that the specific involvement of IL-1δ in skin inflammation was not disclosed in the specification. However, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." Brana, 51 F.3d at 1568, 34 USPQ2d at 1442.

Here, once IL-1δ is accepted as a mediator of inflammation, those skilled in the art would recognize compounds that inhibit IL-1δ to be useful. Granted, some experimentation remains to be done before an IL-1δ-binding compound could be used, for example, in therapy. However, determining whether IL-1δ promotes or inhibits inflammation and which tissue(s) it acts in would seem to be questions more of enablement than of utility. The issue of enablement has not been briefed in this case, but testing different tissues for expression of a single, known gene would not on its face seem to be an undue amount of experimentation for persons skilled in the relevant art.

Summary

The evidence of record supports the specification's disclosure that the claimed products are useful in either inhibiting or promoting inflammation. We therefore reverse the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, for lack of patentable utility.

REVERSED

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